

II. Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 31 and 33-44 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse the rejection and request reconsideration.

The Examiner states that claim 31 and dependent claims 33-44 are indefinite with respect to what constitutes "genetic bit analysis" and what one is "interrogating" for.

The Examiner's attention is respectfully drawn to the fact that the specification at page 15, incorporates by reference Goelet, P. *et al* WO 92/15712. The Applicant respectfully submits that the term "genetic bit analysis" is defined by reference to Goelet *et al* WO 92/15712 and is definite as to just what constitutes "genetic bit analysis." The term has a generic meaning in the art that pertains to the determination of the identification of the nucleotide (i.e., the genetic bit') residing at a particular location in a polynucleotide. It is believed that the term would not be deemed indefinite by those of ordinary skill in the art. In the interests of advancing the prosecution of the present application, Applicants have amended the claim to recite the steps of genetic bit analysis. Support for this amendment can be found in the specification at page 33, line 20 - page 36, line 19. No new matter has been added by this amendment.

Applicants have additionally amended claim 31 to replace the term "interrogating" with the term "identifying," and respectfully submit that the rejections under 35 U.S.C. § 112, second paragraph may now be withdrawn. Support for this amendment may be found in the specification at page 1 (lines 29-33), page 3 (lines 30-1), page 4 (lines 1-2) and page 14 (line 1). No new matter has been added by this amendment.

III Rejection under 35 U.S.C. § 103 in view of Reiss *et al.* and Wheeler *et al.*

The Examiner has rejected claims 30-38 and 42-46 as being unpatentable over Reiss *et al.* and Wheeler *et al.* As understood by Applicants, the essence of the Examiner's rejection is that the combination of Reiss *et al.* and Wheeler *et al.* make

Applicants' invention obvious. The Examiner states that Reiss *et al.* provides a review of the advancements of polymerase chain reaction ("PCR") and its ability to detect numerous diseases in human and that Wheeler *et al.* teaches a number of controls that could be used in such detection. Applicants respectfully traverse the rejection and request reconsideration.

Applicants submit that, even if there were a teaching to suggest that these references could be combined, the combination of these references fails to teach Applicant's invention. Applicants respectfully submit that the combined cited references do not suggest the use of genetic bit analysis to analyze polymorphisms. As such, they fail to render the claimed subject matter, when viewed as a whole, obvious.

Applicants further submit that the present invention provides an approach for identifying previously uncharacterized polymorphic sites. In this regard, the Examiner's attention is respectfully drawn the Summary of the Invention (page 3, lines 27-35). The Examiner's attention is also drawn to Examples 1 and 2 in the specification (pages 45 (line 28) - 50 (line 6)) wherein Applicants identify previously uncharacterized polymorphic sites.

In contrast, the references cited by the Examiner do not teach how an uncharacterized polymorphic site could be identified, and hence do not teach how such sites could be used. Table 1 of Reiss *et al.*, relied on by the Examiner, describes only polymorphic sites that have, at least in part, been characterized. Similarly, Wheeler *et al.* teaches negative and positive PCR controls for use in combination with a known target sequence. As the Examiner will be aware, Wheeler *et al.*, teaches the use of a positive control which includes part of the characterized target DNA and a negative control that totally lacks the characterized sequence. While it is unclear to Applicants which of the Applicants' samples are the "reference" samples referred to by the Examiner as Applicants' controls, Applicants respectfully submit that Wheeler *et al.* fail to teach any method by which a previously unidentified polymorphic site could be identified or the nature of suitable controls that could be utilized in such a process.

It is respectfully submitted that the claims must be assessed as a whole and a finding that some of the features of the invention may have been known does not

support a conclusion that the claimed invention as a whole is obvious. It is respectfully submitted that the rejection may be properly withdrawn.

IV Rejection under 35 U.S.C. § 103 in view of Reiss *et al.* and Wheeler *et al.*, and further in view of Goelet *et al.*

The Examiner has rejected claim 39 as being unpatentable over Reiss *et al.* and Wheeler *et al.* (for the reasons stated above) and further in view of Goelet *et al.* As understood by the Applicants, the essence of the Examiner's rejection is that it would have been obvious to have combined the use of dideoxynucleotides in primer extension reactions as taught by Goelet *et al.* to a method for detecting a polymorphic region of nucleic acid as taught by Reiss *et al.* Applicants respectfully request reconsideration of the rejection.

It is respectfully submitted that while, as stated by the Examiner, Goelet *et al.* teach the use of dideoxynucleotides in primer reactions as a general method for identifying the nucleotide present at a particular site, the document is not believed to teach how polymorphic sites can be detected in the first place.

In contrast, Applicant's present invention discloses that the methods of Goelet can be used to identifying the nucleotide present at a particular site of a polymorphism, and additionally describes methods for detecting new polymorphic regions.

As indicated above, the claims must be assessed as a whole and a finding that some of the features of the invention may have been known does not in itself support a conclusion of obviousness. It is respectfully submitted that the rejection may be properly withdrawn.

V Rejection under 35 U.S.C. § 103 in view of Reiss *et al.*, Wheeler *et al.* and Goelet *et al.*, and further in view of Urdea.

The Examiner has rejected claim 40 and 41 as being unpatentable over Reiss *et al.*, Wheeler *et al.* and Goelet *et al.* as applied to claims 30-39 and 42-46 and further in view of Urdea. Applicants respectfully traverse the rejection and request reconsideration.

SENT BY:

8-20-96 ; 3:24PM ;

HOWREY & SIMON

703 305 7401;#12/12

The Examiner states that Urdea teaches the use of a solid support, which has attached to it an oligonucleotide that in turn captures a target nucleic acid that is subsequently used in a primer extension reaction.

Applicants respectfully draw the Examiner's attention to the fact that solid phase attachment is also described in Goelet *et al.*

As discussed above, the Applicants' invention not only provides methods for the identification of the nucleotide present at a single nucleotide polymorphism, but additionally discloses methods for detecting new polymorphisms. These elements of claims 40 and 41 are not believed to be suggested by the combined cited art.

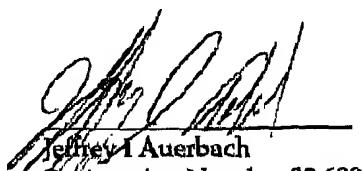
While, as stated by the Examiner, Urdea teaches the use of solid supports, Urdea, even in combination with Reiss *et al.*, Wheeler *et al.*, and Goelet *et al.*, fail to teach the use of GBA in combination with the polymerase chain reaction, as a means to identify single nucleotide polymorphisms using immobilized capture nucleic acids. It is respectfully submitted that the rejection may be properly withdrawn.

Having now fully responded to the outstanding objections and rejections, Applicants respectfully submit that the present application is in condition for Allowance. Applicants earnestly solicit early notice of such favorable action.

The Examiner is invited to contact the undersigned at (202) 383-7451 with respect to any issue in this application.

Respectfully submitted,

Date: 12/1/95
Howrey & Simon
1299 Pennsylvania Ave., N.W.
Washington, D.C. 20004



Jeffrey I. Auerbach
Registration Number 32,680
Attorney for Applicants